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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
LACOURCIERE, K	
ART UNIT	**PAPER NUMBER**
1635	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/215,257	FIRE ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 39-46* is/are pending in the application.

4a) Of the above claim(s) *7 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-23,25-35 and 39-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. This application contains claims 7 and 24 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

2. Newly submitted claims 43-46 are generic and will be examined only to the extent that they read on the elected subject matter.

Claim Rejections - 35 USC § 112

3. The rejection of record of claims 1-6, 8-23, 25-35, 39, 40 under 35 U.S.C. 112, second paragraph as set forth in the prior Office action (mailed 02-14-01) has been withdrawn in response to Applicants' amendments (filed 08-14-01).

The rejection of record of claim 40 under 35 USC 112, first paragraph, is withdrawn in response to Applicants' arguments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10-23, 27-35, 41 and 42 are maintained as rejected and new claims 43-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting expression of a target gene using a double stranded RNA in nematode or in vitro, does not reasonably provide enablement for methods of inhibiting expression of a target gene using a double stranded RNA in any organism in vivo (whole organism). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection was set forth in the prior Office action (mailed 02-14-01) and is set forth below with modifications to reflect Applicants' amendments filed 08-14-01.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-6, 10-23, 27-35 and 41-46 are drawn broadly to methods of inhibiting gene expression in any setting, in vitro or in vivo(whole organism), for any organism, including humans and other mammals. The claimed methods are further drawn to methods wherein the double stranded RNA of the claimed methods is administered by various routes, including injection, administration at a body cavity and by administering the double stranded RNA in food, including administering a transgenic organism which has been genetically manipulated to produce the

double stranded RNA from a vector or producing the double stranded RNA in the target organism by expression of the double stranded RNA from a vector, which read on gene therapy methods.

The specification provides examples wherein double stranded RNA, with regions corresponding to several different target genes, is administered to C. elegans through various routes and the target gene is thereby inhibited. Applicant has provided a number of post-filing references which demonstrate similar methods applied to reduce expression of a variety of genes in drosophila. The specification does not provide any examples wherein their claimed methods are used to inhibit the expression of any gene in a mammal, including humans.

Methods of inhibiting gene expression using nucleic acids in vivo(whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene., gene therapy methods (ie. nucleic acids expressed from a vector) are further hampered by unpredictable loss of expression (see for example Branch, Crooke, Anderson and Verma et al.). The specification states that the claimed methods differ from antisense methods by acting through a different, but undefined, mechanism. Despite the mechanism, the methods claimed require that an RNA, or vector expressing said RNA, be delivered specifically to a target cell in an organism in vivo(whole organism) at a concentration effective enough to inhibit the expression of a target gene, particularly at a concentration effective

enough to inhibit the expression of a gene to the extent that the organism exhibits a "loss of function" phenotype. As such, although Branch, Agrawal(TIBTech), Verma et al. and Anderson discuss issues of delivery and expression in reference to antisense methods and gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. Specific embodiments of the claimed methods include delivery of the RNA of the claimed methods using food, including food comprising an organism expressing the RNA. This method of delivery would not be predicted to be effective, particularly in mammals, because the RNA would be degraded by digestive enzymes. The specification provides generic guidance with respect to delivery of double stranded RNA molecules, or vectors expressing such, into a cell in vivo(whole organism), however, the specification does not provide specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of nucleic acids (or vectors) to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid.

Applicant has provided numerous post-filing references which support their assertion that the claimed methods can be applied successfully to a range of genes in several different organisms, particularly C. elegans, drosophila and other invertebrates. However, other examples demonstrate that in other organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. (reference on PTO form 1449 filed 12-04-00) or Wianny et al. (reference on PTO 1449, filed 12-04-00)). Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the

embryonic stage have demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions(see for example Wianny et al.). Further, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA in vivo(whole organism) and in Xenopus an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74). This suggests that although post-filing references support the enablement of the claimed methods more broadly than the working examples presented in the instant specification, the claimed methods are not enabled over the full scope claimed. Metabolic differences between different organisms would not allow one skilled in the art to broadly apply the methods taught for C. elegans and other invertebrates successfully in every organism, particularly mammals.

To practice the methods claimed, over the full scope claimed, it would require undue trial and error experimentation for the skilled artisan. Such experimentation would include the determination of how to specifically deliver a double stranded RNA or a vector to a target cell at a concentration effective enough to inhibit the expression of a target gene or inhibit a gene to the extent that the phenotype is loss of function, the determination of an appropriate vector and enhancer-promoter combination for each target cell type "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response, how to prevent the transient

inhibition of genes observed in embryo experiments, and the determination of how to implement these methods in organisms with dsRAD activity (and if these methods can be used at all).

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art (beyond invertebrates), the high level of unpredictability in the art, the lack of specific guidance by the inventor (beyond C. elegans), the lack of working examples (beyond C.elegans), and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The rejection of record of claims 1, 4-6,11, 13, 21, 22, 23, 31 and 34 under 35 U.S.C. 102(e) as being anticipated by Draper et al. as set forth in the prior Office action (mailed 02-14-01) is withdrawn in response to Applicants' amendments filed 08-14-01. The claims are now limited to methods wherein the double stranded region of the RNA comprises the region corresponding to the target gene sequence and the complement of said sequence, however the RNA molecules disclosed by Draper et al. comprise a single stranded RNA region which corresponds to the sequence of the target gene.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1- 6, 8-11, 13, 17, 18, 22, 23, 25, 26, 28, 30, 31, 40 and 41 are maintained as rejected and new claims 43-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550) for the reasons of record set forth in the prior Office action (mailed 02-14-01). This rejection is set forth below, with modifications that reflect Applicants' amendments filed 08-14-01.

Agrawal et al. disclose methods of inhibiting the expression of a target gene in a cell, including a cell in vivo(whole organism), by administering an RNA molecule comprising a double stranded RNA wherein one strand is complementary to a sequence from a target gene further comprises the complement of the target hybridizing region, and would, therefore, comprise and RNA sequence which is corresponds to the nucleotide sequence of a target gene. Agrawal et al. disclose their method wherein each region (the complement and the corresponding sequence) are at least 25 nucleotides long. Agrawal disclose their methods wherein the target gene is a cellular gene, an endogenous gene, and a viral gene, including a viral gene which has been incorporated

into the host genome, which would be encompassed by the term "transgene". Agrawal further disclose their methods wherein the cell is from an invertebrate, including a nematode (see for example p 18, line 33), wherein the each of the complementary and corresponding nucleotide sequence is 50 nucleotides long (see for example page 15, line 30) and wherein the expression of the target gene in a cell (in vitro) is inhibited by at least 10% (see for example experiments 1-3). Agrawal et al. provide for methods wherein the RNA is administered by extracellular injection or administered to a body cavity, outside the cell (see for example page 18, line 9).

The specification seems to indicate all cells are susceptible to RNA interference, and further "RNA interference" would encompass antisense RNA interference, and, therefore, Agrawal et al. disclose their methods in cells and organisms susceptible to RNA interference.

The specification has not defined the term "stably anneal" (see the rejection under 35 USC 112, second paragraph), but the dsRNA molecules disclosed by Agrawal et al. is disclosed as annealing to form a dsRNA structure and, therefore, would be encompassed by the term "stably annealed", particularly since the molecules disclosed by Agrawal et al. have long stretches of complementary nucleotides.

Therefore, Agrawal et al. anticipates claims 1- 6, 8-11, 13, 17, 18, 22, 23, 25, 26, 28, 30, 31, 40, 41 and 43-46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 39 is maintained as rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al., for the reasons of record set forth in the prior Office action (mailed 02-14-01).

This rejection is set forth below, with modifications that reflect Applicants' amendments filed 08-14-01.

Claim 39 is drawn to a kit comprising means for introducing RNA into a cell and comprising a double stranded RNA. Agrawal et al. teach means for introducing RNA into a cell and teach a double stranded RNA, as claimed. Agrawal et al. do not claim the RNA and the means for introducing together in a kit. It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to put the reagents taught by Agrawal et al. together in a kit because Agrawal et al. teach using these reagents together. One of ordinary skill in the art would have been motivated to make a kit comprising the double stranded RNA and the means for introducing RNA into a cell, as taught by Agrawal, for ease of use and convenience. Therefore, the invention of claim 39 would have been obvious, as a whole, to one of ordinary skill in the art at the time the invention was made based on the teachings of Agrawal et al.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6, 8-21, 39, 40, 41 and 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 39, 40, 41 and 43-46 recite the limitation wherein the complementary regions of the dsRNA "stably anneal". The term "stably" is a term of degree, which is not defined in the specification. One skilled in the art could not determine what degree of stability (e.g. under what conditions an RNA must remain hybridized) to be considered "stably annealed". Claims 2-6 and 8-21 are indefinite for the same reasons due to their dependence on claim 1.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 8-21, 39, 40, 41 and 43-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 39, 40 and 41 have been amended to recite the limitation wherein the complementary regions of the dsRNA "stably anneal". Newly submitted claims 43-46 also include the limitation wherein the complementary regions of the dsRNA "stably anneal". Support for the limitation wherein the complementary regions of the dsRNA "stably anneal" could not be found in

the application as filed. Claims 2-6 and 8-21 are rejected for the same reasons due to their dependence on claim 1.

Claim 43 includes the limitation "the RNA is not a ribozyme". Support for the limitation "the RNA is not a ribozyme" could not be found in the application as filed.

Claim 44 includes the limitation "the dsRNA is not a ribozyme". Support for the limitation "the dsRNA is not a ribozyme" could not be found in the specification as filed.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. in view of Mercola et al.(Cancer Gene Therapy, Vol 2, No 1, 1995).

Claim 21 is drawn to a method of inhibiting the expression of a target gene in a cell comprising introducing a dsRNA into a cell, wherein the dsRNA is expressed in a vector, and wherein the RNA comprises a region of at least 25 nucleotides complementary to the target gene

and further comprises a region which corresponds to the sequence of the target DNA and wherein the two regions stably anneal to each other.

Agrawal et al. teach methods of inhibiting the expression of a target gene in a cell, including a cell in vivo(whole organism), by administering an RNA molecule comprising a double stranded RNA wherein one strand is complementary to a sequence from a target gene further comprises the complement of the target hybridizing region, and would, therefore, comprise and RNA sequence which is corresponds to the nucleotide sequence of a target gene. Agrawal et al. disclose their method wherein each region (the complement and the corresponding sequence) are at least 25 nucleotides long. The specification seems to indicate all cells are susceptible to RNA interference, and further "RNA interference" would encompass antisense RNA interference, and, therefore, Agrawal et al. teach their methods in cells and organisms susceptible to RNA interference. The specification has not defined the term "stably anneal" (see the rejection under 35 USC 112, second paragraph), but the dsRNA molecules taught by Agrawal et al. are taught as annealing to form a dsRNA structure and, therefore, would be encompassed by the term "stably annealed", particularly since the molecules disclosed by Agrawal et al. have long stretches of complementary nucleotides.

Agrawal et al. do not teach their nucleotide as expressed in a vector in the cell.

Mercola et al. teach expressing antisense RNA in a vector.

It would have been obvious to one of ordinary skill in the art to express the nucleotide taught by Agrawal et al. in a vector, as taught by Mercola et al. because expression of RNA,

including antisense, was well known in the art at the time the instant invention was made (as exemplified by Mercola et al.). One of ordinary skill in the art would have been motivated to express the nucleotide molecule taught by Agrawal et al. in a vector because expressing RNA is less expensive than synthesis, provides a high concentration of RNA in a target cell and, as taught by Mercola et al. (see for example p 56 Summary) expression of antisense in a vector in stable cell lines are beneficial as preliminary studies for in vivo (whole organism) methods. One of ordinary skill in the art would have reasonably expected to be successful at expressing the RNA taught by Agrawal et al. and inhibiting expression of a target molecule in vitro (cell culture) because in vitro RNA expression was routine.

Therefore, at the time the instant invention was made, the invention of claim 21 would have been obvious to one of ordinary skill in the art, as a whole.

Claim Objections

9. Claim 44 is objected to because of the following informalities: The word "and" is missing before the phrase "the dsRNA is not a ribozyme" in the last line of the claim. Appropriate correction is required.

Response to Arguments

10. Applicant's arguments filed 08-14-01 have been fully considered but they are not persuasive.

Applicant argues (page 6 of the response filed 08-14-01) that the instantly claimed methods are distinguished from the ribozyme art cited in the prior Office action (mailed 02-14-01) because RNA interference requires protein cofactors, whereas ribozymes do not. Further, Applicant argues that the specification describes the invention as different than methods of genetic interference in the prior art. These arguments have not been found to be persuasive because Applicant is arguing a limitation not found within the claimed methods, the methods claimed do not recite protein cofactors. Further, although Applicant asserts in their specification that the claimed methods do not encompass methods known in the prior art , the claims do encompass methods disclosed in the prior art, as evidenced by the prior art references cited in the rejections of record.

Applicant argues, in response to the rejection of record of claims 1-6, 10-23, 27-35 and 40 under 35 USC 112, first paragraph (set forth in the prior Office action mailed 02-14-01) that the examiner has not provided specific technical reasons why one skilled in the art would require undue experimentation to practice the methods claimed over the full scope claimed. This is not found to be persuasive because the Examiner has provided technical reasons for why undue experimentation would be required on the part of the skilled artisan in the rejection of record (set forth in the prior Office action mailed 02-14-01 and repeated herein). For example, the problems with delivery of dsRNA, delivery of vectors, sustained expression of vectors, the choice of cell specific vectors and promoters to achieve and maintain expression, and immune system responses.

Applicant argues that the problems encountered in gene therapy as cited by the Examiner

are not applicable to the claimed methods. Applicant states that transient RNA interference and interference in a subpopulation of cells is adequate for functional genomic studies, the RNA of the claimed methods can be delivered by electroporation and direct injection, the double stranded structure stabilizes the RNA and the dosage of RNA is much lower than the dosage required for antisense or gene therapy methods. Applicant argues that the transient inhibition demonstrated by Svoboda et al. and Wianny et al. (cited by the Examiner to support the unpredictability of RNA-mediated interference in mammals) was expected because the dsRNA was microinjected and cell division resulted in dilution of the dsRNA. These arguments have not been found persuasive because the issues cited by the Examiner do apply to the claimed methods when practiced over the full scope claimed, for example, when practiced in vivo(whole organism), because the claimed methods encompass methods which require the delivery of nucleic acids to a target cell within a whole organism, and further require the delivery and sustained expression of a vector in a target cell in a whole organism, at a level which will inhibit a target gene enough to produce a loss of function phenotype. Although Applicant argues that transient interference and inhibition in a subpopulation of cells is adequate for genomic studies, this does not address the full scope of the claimed methods and is not applicable to in vivo(whole organism) (particularly mammals) methods or methods wherein a loss of function phenotype in a whole organism (for example a mammal) is claimed. Electroporation and direct injection are not feasible methods of delivery for the full scope claimed, for example whole organisms, or mammals (beyond oocytes and embryos). Although Applicant states that the required amount of dsRNA required to be delivered for the

claimed methods is lower than that required for antisense and gene therapy methods, Applicant has not provided guidance to the skilled artisan that would enable the delivery and expression of dsRNA in vivo (whole organism) at a level required for dsRNA inhibition.

Applicant argues that Although results in zebrafish have been equivocal, it is unreasonable to ignore positive results in favor of negative results. Applicants cite Oates et al. (cited by Examiner in the rejection of record) and state that Oates et al. could not reproduce the positive results of Li et al. Applicant argues that despite scattered negative reports, the weight of evidence demonstrates that dsRNA interference works in a wide variety of organisms. These arguments have not been found to be persuasive because the lack of reproducibility (as demonstrated by Oates et al., a skilled artisan) supports the unpredictability. The positive results have not been ignored, it is just recognized that achieving positive results is not predictable because the claimed methods have unreliable positive and negative outcomes when practiced in various in vivo settings. Applicants have not provided guidance that would enable the skilled artisan to overcome the technical problems to practicing these methods in a predictable manner in vivo.

Applicant argues that the complications resulting in organisms with an immune system or panic response can be avoided by using conditions like shorter lengths or lower concentrations. Applicant cites Elbashir et al., Bass and Caplen et al. as demonstrating that shorter RNA's can overcome the issues of inducing the interferon response. These arguments have not been found persuasive because the claimed methods are directed to dsRNA which is 25 bases or longer and the specification contemplates dsRNA as long as 500 nucleotides. The references cited are

directed to dsRNA shorter than the oligonucleotides claimed, for example, dsRNA which is 21 and 22 nucleotides long (for example Elbashir et al.) and a maximum of ~25 nucleotides (for example Caplen et al.). Further, the dsRNA described by Elbashir et al., Bass and Caplen et al. are structurally different than the oligonucleotides used in the claimed methods and described in the specification. The dsRNA used by Elbashir et al., Bass and Caplen et al. have, for example, a 2 base 3' overhang. The short length (ie. less than 25 nucleotides) and 3'overhang were not recognized in the instant specification as a structural feature required to enable the claimed methods, nor were these features appreciated by the art at the time the instant application was filed and, therefore, do not support the enablement of the claimed invention. Elbashir et al., Bass and Caplen et al. support the lack of enablement for methods of dsRNA interference in vertebrates at the time the instant application was filed.

Applicant argues that the amendment to the claimed methods wherein the cell or organism is susceptible to RNA interference overcomes this rejection. This is not found to be persuasive because the instant specification seems to indicate that all cells are susceptible to RNA interference.

Applicant argues in response to the rejection of record under 35 USC §102 of claims 1-6, 8-11, 13, 17-18, 22-23, 25-26, 28, 30-31 and 40 (set forth in the prior Office action mailed 02-14-01 and repeated herein) as anticipated by Agrawal et al. (WO 94/01550) that Agrawal et al. does not teach all the limitations of the claims. Applicant applies these same arguments to the

rejection of record (set forth in the prior Office action mailed 02-14-01 and repeated herein) of claim 39 under 35 USC §103(a) as obvious in view of Agrawal et al. Applicant argues that Agrawal et al. teaches their double stranded RNA as a structure that provides resistance to degradation and that the structure is not integral to the antisense function of their oligonucleotide. Applicant argues that Agrawal et al. disclose the mechanism of their methods as a single strand of the dsRNA interacting with the target. Applicant argues that the mechanism suggested by Agrawal et al. would suggest that the overlaps between the target and self-complementary region would be short to allow disruption and replacement to occur. Applicant argues that the instant claims recite that the RNA "comprises" or "consists essentially of" the double stranded structure so a functional single strand in the RNA disclosed by Agrawal et al. is not anticipatory. Applicant cites Parrish et al. (post-filing reference) as demonstrating that a specific chemical structure is required for RNA interference: natural or modified ribonucleotides, whereas Agrawal et al. do not indicate a preference for RNA over DNA.

These arguments have been considered, but are not found to be persuasive. The methods disclosed by Agrawal et al. meet all of the limitations of the claimed methods. The mechanism of action does not distinguish the claimed methods from the methods disclosed in Agrawal et al. because all the steps in the claimed methods are the same as the methods disclosed by Agrawal et al. The dsRNA disclosed by Agrawal et al. include RNA wherein the regions of complementarity is extensive, including, for example, wherein the region of self complementarity is "so extensive as to involve every nucleotide of the oligonucleotide" (see for example page 15, line 27-28) and

contemplate up to 50 nucleotides of self-complementarity. This RNA meets the limitations of the claimed invention. Agrawal et al. does not indicate a preference for RNA over DNA, however, Agrawal et al. does disclose RNA which meets all the limitations of the claimed invention and, therefore, is anticipatory, and provides the limitations required for obviousness.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523. The Examiner can normally be reached 8:30 am to 6:30 pm Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
October 18, 2001

SEAN McGARRY
PRIMARY EXAMINER